31. (Amended) The apparatus of Claim 1, wherein the thermal insulating material is plastic and said temperature monitor is an integrated resistive thermal detector molded into said plastic.

32. (Amended) The apparatus of Claim 1, wherein the thermal insulating material is plastic and said temperature monitor is a thermocouple molded into said plastic.

Please add the following new claim:

--33. (New) The apparatus of Claim 1, wherein each of said heaters comprise conductive coils forming loops around each of said well structures along a length of said well structures.--

REMARKS

Claims 1, 2, 6-8, 10-12, 14-23, 26-33 are pending in the application. Support for the amendment to the specification is found throughout the specification and particularly on page 3, lines 10-12 where U.S. Serial Nos. 09/337,086 and 09/235,081 are incorporated by reference. Support for the amendments to claim 1 is found on page 7, lines 10-12 and lines 25-26; and page 10, lines 18-10. Support for new claim 33 is found on page 10, lines 23-25 and Fig. 4B.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with markings to show changes made." For the Examiner's convenience a clean copy of the currently pending claims is appended hereto as Appendix A.

The Examiner objected to the drawings under 37 CFR 1.83(a). The Examiner stated that the means for delivering reagents in claims 24 and 25 must be shown or the feature(s) canceled from the claim(s). Applicant has cancelled claims 24 and 25, bringing the drawings into compliance with 37 CFR 1.83(a).

Claims 1-32 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that it is unclear as to how each of the elements of the apparatus in claim 1 are structurally connected to one another. Applicant has amended claim 1 to recite an apparatus comprising "a supporting substrate comprising a ceramic layer and comprising channels and vias defining a plurality of separate well structures separated by thermal insulating material". Applicant submits amended claim 1 clearly states that the ceramic device comprises wells separated by insulating material.

The Examiner further states that claims 5 and 9 are unclear, noting that claims 5 and 9 specify a process of making the apparatus, i.e. by ceramic multilayer technology, a process claim which is dependent on claim 1 , an apparatus claim. The Examiner states that claims 5 and 9 are accorded no patentable weight as process limitations do not add patentability to an apparatus structure which is not distinguished from the prior art. Without admitting the propriety of the rejection, claims 5 and 9 have been deleted.

Applicant respectfully submits that the amended claims are in compliance with 35 U.S.C. §112, and asks that the Examiner reconsider and withdraw the §112 rejections.

Claims 1-4, 6-8, 10, 13, 14, 17-26, and 28-32 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hayes et al. in view of Kroy et al.

Hayes et al. recite a method for making an apparatus to conduct biochemical analyses. The apparatus is fabricated using flex circuit manufacturing techniques (see column 7, lines 28-

45) and provides a plurality of wells 40-42 that may have a heater 50-52, cooler 90, or temperature monitor 182. Flex circuit manufacturing techniques involve assembling a device composed of a series of layers, some metallic and some non-metallic. All conductive structures in the apparatus disclosed by Hayes are confined to the two-dimensional 'metallic' layers. As the Examiner acknowledges, Hayes does not disclose a device manufactured from a ceramic material.

Kroy et al. disclose a micromechanical structure which may be fabricated from ceramic materials using masking and etching techniques. The structure disclosed by Kroy comprises a substrate with canals or depressions fitting with a second substrate comprising humps to form a plurality of wells. The masking and etching techniques employed by Kroy restrict practically achievable conductive paths to a two-dimensional plane.

In contrast, Applicant's amended claim 1 recites an apparatus comprising "conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors."

Applicants note that three criteria must be met to establish a prima facie case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. §2142).

The Examiner suggests that Applicant's invention would result from combining the apparatus disclosed by Hayes with the ceramic material disclosed by Kroy. The Examiner suggests the motivation to use a ceramic material in the fabrication of the apparatus taught by Hayes would have been to facilitate effective thermal isolation of each of the wells. The

Examiner further observes that ceramics are known corrosion resistant and heat-resistant, or thermally nonconductive, insulative materials. Since the courts have held that the selection of a known material based upon the suitability of the material is within the ambit of one of ordinary skill in the art (In re Leshin, 125 USPQ 416 (CCPA 1960)), the Examiner concludes it would have been obvious to fabricate the substrate of the device from a ceramic material.

Applicants submit, however, that the references taken alone or in combination fail to teach or suggest all the limitations of amended claim 1, namely a device having "conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors." As discussed above, Hayes et al. does not teach or disclose a three-dimensional conductive pathway. For example, in Fig. 4B of the present disclosure (claim 33), the heating element winds around the well throughout its length. In contrast, Fig. 4 of Hayes et al. depicts the presence of a heater above 154 or below 154' the well 160. Kroy does not disclose or suggest integrating conductive paths within the device. Heating and cooling elements disclosed by Kroy are limited to canals etched in a substrate (col. 4, lines 26-31, Fig. 7) or Joule-Thomson coolers comprising canals (col. 9 line 15-col. 10 line 19). Therefore, neither reference by itself suggests a device with a three-dimensional conductive pathway. Indeed, such a device would be impractical to make utilizing the flex circuit manufacturing or etching and masking techniques disclosed by Hayes and Kroy respectively.

Taken together, the references also fail to suggest or motivate the claimed invention, as both references cite their manufacturing techniques as an advantage, they together teach away from employing a technique that would allow for three-dimensional conductive pathways. A reference which leads one away from the claimed invention cannot render the invention obvious. See Dow Chemical v. American Cyanamid, 2 USPQ 2d 1350 (Fed. Cir. 1987).

Hayes et al. and Kroy et al. taken alone or in combination not disclose all limitations in amended claim 1. Accordingly, the 35 U.S.C. §103(a) rejections of claim 1, and claims 2, 6-8, 10, 13, 14, 17-23, 26, and 28-32 depending from base claim 1 should be withdrawn.

Additionally, regarding claims 17 and 18, the Examiner suggests Hayes et al. recite an apparatus controlled using a programmable controller. The Examiner argues that one of ordinary skill in the art would have contemplated a row and column addressing or an individual electrical addressing system.

However, it is the three-dimensional conductive paths provided in amended claim 1 that facilitate an addressing scheme in the present invention. For example, the layer-by-layer flex circuit technology employed by Hayes results in well structures with heaters having interconnects 852a and 852b (Hayes Fig. 10). Creating a column-and-row arrangement of wells and interconnects in the process disclosed by Hayes would require a complex arrangement of heating elements, and a low density of wells to provide more space between heater lines. In contrast, one embodiment of Applicant's invention provides heaters coiling around the well for its entire length, emerging at the surface of the device in accessible interconnects (Fig. 4B). Applicant has accordingly added claim 33, reciting a heater for heating each well comprising "conductive coils forming loops around each of said well structures along a length of said well structures." Creating a row-and-column addressable array is consequently simple, as all heaters can be accessed from the top plane and need not interfere with one another.

Taken separately or together, the disclosures of Hayes or Kroy, et al. do not suggest or motivate three-dimensional conductive paths, as in amended claim 1, that facilitate an addressable array of wells. Accordingly, the 35 U.S.C. §103(a) rejections of claims 17 and 18 depending from base claim 1 should be withdrawn.

Claims 11 and 12 were rejected under 35 U.S.C. §103(a) over Hayes et. al. in view of Kroy et. al. and further in view of Anderson et al.

Hayes et al. and Kroy et al. are discussed above.

Anderson et al. is directed toward a miniaturized genetic analysis system. As the Examiner points out, Anderson discloses the coating of surfaces with parylene. The devices of Anderson are fabricated with conventional microfabrication techniques (col. 18, line 58-col. 20, line 17).

As the Examiner is aware, a §103 rejection requires that the references alone, or in combination, disclose all the limitations of the pending claim (see MPEP §2142).

The Examiner argues that it would have been obvious to use parylene as a coating for the well structures. However, the combination of Hayes, Kroy, and Anderson references fail to disclose all the features of Applicant's amended claim 1 including a device comprising "conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors." The conventional microfabrication techniques disclosed by Anderson preclude fabricating three-dimensional conductive pathways.

Accordingly, the combination of Hayes et al., Kroy et al., and Anderson et al. do not disclose all limitations of claims 11 and 12, depending from claim 1 and the rejection under 35 U.S.C. §103 should be withdrawn.

Claims 15 and 16 were rejected under 35 U.S.C. §103(a) over Hayes et al. and Kroy et. al. and further in view of Burns et al.

Hayes et al. and Kroy et al. are discussed above.

Burns et al. is directed toward microscale devices. Burns, as Anderson above, discloses the use of conventional planar microfabrication technologies (col 10 line 51- col 12 line 48).

As the Examiner is aware, a §103 rejection requires that the references alone, or in combination, disclose all the limitations of the pending claim (see MPEP §2142).

The Examiner argues that it would have been obvious to integrate a metal wire resistive heating element to heat the well structures. However, the combination of Hayes, Kroy, and Burns references fail to disclose all the features of Applicant's amended claim 1 including a device comprising "conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors." The conventional microfabrication techniques disclosed by Burns preclude fabricating three-dimensional conductive pathways.

Accordingly, the combination of Hayes et al., Kroy et al., and Burns et al. do not disclose all limitations of claims 15 and 16, depending from claim 1 and the rejection under 35 U.S.C. §103 should be withdrawn.

Claim 27 was rejected under 35 U.S.C. §103(a) over Hayes et al., Kroy et al., and further in view of Anderson et al.

Hayes et al., Kroy et al., and Anderson et al. are discussed above.

As the Examiner points out, Anderson et al. does teach the use of mineral oil as a sealing means. However, as detailed above, the combination of Hayes et al., Kroy et al., and Anderson et al. do not teach, motivate, or suggest the features in amended claim 1. Therefore, the §103(a) rejection of claim 27, depending from base claim 1, should be withdrawn.

In conclusion, none of the cited references, taken either alone or in combination, discloses or suggests all limitations of the claimed invention. Accordingly, the applicants submit that the claims are now in condition for allowance and an early notification of such is earnestly solicited.

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The Examiner is invited to telephone the undersigned attorney in the event that further issues are identified that would preclude allowance of the claims.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) An apparatus for performing parallel, independently controlled molecular reactions, comprising:

(a) a supporting substrate comprising a ceramic layer,

(b) said substrate comprising channels and vias defining a plurality of separate well structures [comprising a thermal conducting layer and wherein the well structures are] separated by [a] thermal insulating [layer] material,

(c) a heater associated with each [a means for heating each] well structure [in thermal contact with the thermal conducting layer comprising each well],

(d) a cooling element associated with [a means for cooling] each well structure [in thermal contact with the thermal conducting layer comprising each well, and]

(e) a temperature monitor associated with [a means for monitoring the temperature of the contents of] each well structure [in thermal contact with the thermal conducting layer comprising each well]; and

(f) conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors.

2. (Unchanged) The apparatus of Claim 1, wherein the molecular reaction is polymerase chain reaction.

Please delete claims 3-5 without prejudice or disclaimer.

6. (Amended) The apparatus of Claim 1, wherein [the thermal conducting layer of the well structures contain] said heater is a resistive heater.

7. (Amended) The apparatus of Claim 6, wherein the well structures are made of a thermal conducting material and are separated by [a] said thermal insulating material.

8. (Amended) The apparatus of Claim 7, wherein [the] said thermal insulating material is glass, silicon, plastic, air contained in an air channel positioned proximal to the well structure, or ceramic.

Please delete claim 9 without prejudice or disclaimer.

10. (Amended) The apparatus of Claim [6] 7, wherein the thermal conducting material is undoped silicon, modified plastics, silver, silver palladium, copper, nickel-molybdenum, platinum, or gold and the thermal insulating material is glass, silicon, plastic, ceramic, or air contained in an air channel positioned proximal to the well structure.

11. (Amended) The apparatus of Claim 1, wherein the well structures are coated with a compound that enhances biocompatibility between the components of the molecular reaction and [the] said [thermal insulating or conducting material comprising the] well structures.

12. (Unchanged) The apparatus of Claim 11, wherein the compound coating is parylene.

Please delete claim 13 without prejudice or disclaimer.

14. (Amended) The apparatus of Claim [13] 1, wherein [the integrated heating system] said heater is a thin film resistive heater.

15. (Amended) The apparatus of Claim [13] 1, wherein [the integrated heating system] said heater is a metal wire resistive heater.

16. (Amended) The apparatus of Claim 15, wherein [the] said metal wire resistive heater is integrated into [the thermal insulating material comprising the] said supporting substrate.

17. (Amended) The apparatus of Claim [13] 14 or 15 or 33, wherein [the integrated heating system utilizes] said heaters are controlled using column-and-row electrical addressing.

18. (Amended) The apparatus of Claim [13] 14 or 15 or 33, wherein [the integrated heating system utilizes] said heaters are controlled using individual electrical addressing.

19. (Amended) The apparatus of Claim 1, wherein [the means for cooling each well structure] said cooling element is a passive cooling system.

20. (Amended) The apparatus of Claim 1, wherein [the means for cooling each well structure] said cooling element is an active cooling system.

21. (Amended) The apparatus of Claim 20, wherein [the] said active cooling system is an integrated cooling system.

22. (Amended) The apparatus of Claim 21, wherein [the] said integrated cooling system is selected from the group consisting of [comprises] a metal plate, an array of metal discs, and a thermo-electric cooler, wherein [the] said integrated cooling system is in thermal contact with each of the well structures.

23. (Unchanged) The apparatus of Claim 1, wherein [the means for monitoring the] said temperature monitor [of the molecular reactions in each well structure] is an integrated optical or electrochemical sensor system.

Please delete claims 24 and 25 without prejudice or disclaimer.

26. (Unchanged) The apparatus of Claim 1, further comprising sealed well structures.

27. (Unchanged) The apparatus of Claim 26, wherein the well structures are sealed using a layer of mineral oil.

28. (Unchanged) The apparatus of Claim 26, wherein the well structures are sealed using a cover.

29. (Amended) The apparatus of Claim 28, wherein the cover further comprises a heater [means for heating the well structures].

30. (Amended) The apparatus of Claim 28, wherein said heater [the means for heating the well structures] is an integrated heating system.

31. (Amended) The apparatus of Claim [4] 1, wherein the thermal insulating material is plastic and [the means for monitoring the] said temperature monitor [of the contents of each well structure] is an integrated resistive thermal detector [which can be] molded into [the] said plastic.

32. (Amended) The apparatus of Claim [4] 1, wherein the thermal insulating material is plastic and [the means for monitoring the] said temperature monitor [of the contents of each well structure] is a[n] thermocouple [which can be] molded into [the] said plastic.

Please add the following new claim:

--33. (New) The apparatus of Claim 1, wherein each of said heaters comprise conductive coils forming loops around each of said well structures along a length of said well structures.--

Appendix A

PENDING CLAIMS

1. An apparatus for performing parallel, independently controlled molecular reactions, comprising:

(a) a supporting substrate comprising a ceramic layer,

(b) said substrate comprising channels and vias defining a plurality of separate well structures separated by thermal insulating material,

(c) a heater associated with each well structure,

(d) a cooling element associated with each well structure,

(e) a temperature monitor associated with each well structure; and

(f) conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors.

2. The apparatus of Claim 1, wherein the molecular reaction is polymerase chain reaction.

6. The apparatus of Claim 1, wherein said heater is a resistive heater.

7. The apparatus of Claim 6, wherein the well structures are made of a thermal conducting material and are separated by said thermal insulating material.

8. The apparatus of Claim 7, wherein said thermal insulating material is glass, silicon, plastic, air contained in an air channel positioned proximal to the well structure, or ceramic.

10. The apparatus of Claim 7, wherein the thermal conducting material is undoped silicon, modified plastics, silver, silver palladium, copper, nickel-molybdenum, platinum, or gold and the thermal insulating material is glass, silicon, plastic, ceramic, or air contained in an air channel positioned proximal to the well structure.

11. The apparatus of Claim 1, wherein the well structures are coated with a compound that enhances biocompatibility between the components of the molecular reaction and said well structures.

12. The apparatus of Claim 11, wherein the compound coating is parylene.

14. The apparatus of Claim 1, wherein said heater is a thin film resistive heater.

15. The apparatus of Claim 1, wherein said heater is a metal wire resistive heater.

16. The apparatus of Claim 15, wherein said metal wire resistive heater is integrated into said supporting substrate.

17. The apparatus of Claim 14 or 15 or 33, wherein said heaters are controlled using column-and-row electrical addressing.

18. The apparatus of Claim 14 or 15 or 33, wherein said heaters are controlled using individual electrical addressing.

19. The apparatus of Claim 1, wherein said cooling element is a passive cooling system.

20. The apparatus of Claim 1, wherein said cooling element is an active cooling system.

21. The apparatus of Claim 20, wherein said active cooling system is an integrated cooling system.

22. The apparatus of Claim 21, wherein said integrated cooling system is selected from the group consisting of a metal plate, an array of metal discs, and a thermo-electric cooler, wherein said integrated cooling system is in thermal contact with each of the well structures.

23. The apparatus of Claim 1, wherein said temperature monitor is an integrated optical or electrochemical sensor system.

26. The apparatus of Claim 1, further comprising sealed well structures.

27. The apparatus of Claim 26, wherein the well structures are sealed using a layer of mineral oil.

28. The apparatus of Claim 26, wherein the well structures are sealed using a cover.

29. The apparatus of Claim 28, wherein the cover further comprises a heater.

30. The apparatus of Claim 28, wherein said heater is an integrated heating system.

31. The apparatus of Claim 1, wherein the thermal insulating material is plastic and said temperature monitor is an integrated resistive thermal detector molded into said plastic.

32. The apparatus of Claim 1, wherein the thermal insulating material is plastic and said temperature monitor is a thermocouple molded into said plastic.

33. The apparatus of Claim 1, wherein each of said heaters comprise conductive coils forming loops around each of said well structures along a length of said well structures.